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=> file casreact
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FILE CONTENT:1840 - 13 Oct 2007 VOL 147 ISS 17

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*                                                          *
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database compiled under the direction of Professor Dr. Klaus Kieslich.

This file contains CAS Registry Numbers for easy and accurate substance
identification.

=> d que
L1              STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -  AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.
L3            2 SEA FILE=CASREACT SSS FUL L1 (     6 REACTIONS)


=> d l3 1-2 ibib abs fcrd


L3   ANSWER 1 OF 2  CASREACT  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         140:111409  CASREACT
TITLE:                    A novel process to prepare pioglitazone via several
                          novel intermediates.
INVENTOR(S):              Pandey, Bipin; Lohray, Vidya Bhushan; Lohray, Braj
                          Bhushan
PATENT ASSIGNEE(S):       Cadila Healthcare Limited, India
SOURCE:                   PCT Int. Appl., 74 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
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     WO 2004007490      A2   20040122       WO 2003-IN241    20030715
     WO 2004007490      A3   20040325
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
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             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
             PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
             TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

IN	2002MU00648	A	20040424	IN 2002-MU648	20020716
AU	2003272072	A1	20040202	AU 2003-272072	20030715
EP	1521753	A2	20050413	EP 2003-753913	20030715
EP	1521753	B1	20070905		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

AT	372336	T	20070915	AT 2003-753913	20030715
US	2006167061	A1	20060727	US 2005-520166	20051004

PRIORITY APPLN. INFO.: IN 2002-MU648 20020716
WO 2003-IN241 20030715

OTHER SOURCE(S): MARPAT 140:111409
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention discloses a novel and general process to prepare various pyridine substituted 5-[4-[2-(alkyl substituted pyridyl)ethoxy]benzyl]-2,4-thiazolidinone derivs. of general formula I [R = alkyl], and their pharmaceutically acceptable salts. The present invention especially provides a novel process to prepare pioglitazone hydrochloride [R = 5-ethyl], via novel intermediates, i.e. II and III. This process involves lesser number of steps with high yields and uses key solid intermediates, which are operationally simple, and therefore offers opportunities for better com. viability.

RX(1) OF 92 - REACTION DIAGRAM NOT AVAILABLE

L3 ANSWER 2 OF 2 CASREACT COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 126:42525 CASREACT
TITLE: Synthesis and Biological Activity of Metabolites of the Antidiabetic, Antihyperglycemic Agent Pioglitazone
AUTHOR(S): Tanis, Steven P.; Parker, Timothy T.; Colca, Jerry R.; Fisher, Roberta M.; Kletzein, Rolf F.
CORPORATE SOURCE: Department of Discovery Chemistry, Pharmacia and Upjohn Inc., Kalamazoo, MI, 49001, USA
SOURCE: Journal of Medicinal Chemistry (1996), 39(26), 5053-5063
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The authors have developed improved syntheses of pioglitazone metabolites I, II, III, and IV and the putative metabolite ketone V. These entities have been compared in the KKAy mouse model of human type-II diabetes to pioglitazone. Ketone V has proven to be the most potent of these thiazolidinediones in this in vivo assay. When I-V were compared in vitro in the 3T3-L1 cell line to pioglitazone for their ability to augment insulin-stimulated lipogenesis, V was again the most potent compound with I,

II, and IV roughly equivalent to pioglitazone. These data suggest that metabolites I, II, and IV are likely to contribute to the pharmacol. activity of pioglitazone, as had been previously reported for ciglitazone..

RX(4) OF 114 - REACTION DIAGRAM NOT AVAILABLE
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> => file caplus
FILE 'CAPLUS' ENTERED AT 10:47:28 ON 17 OCT 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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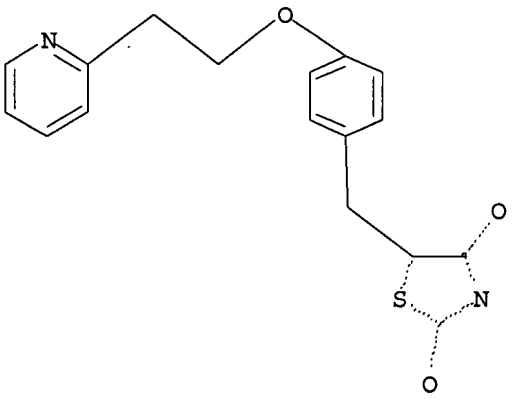
FILE COVERS 1907 - 17 Oct 2007 VOL 147 ISS 17
FILE LAST UPDATED: 16 Oct 2007 (20071016/ED)

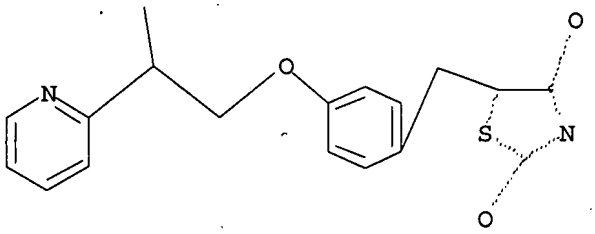
Effective October 17, 2005, revised CAS Information Use Policies apply. They are available for your review at:

http://www.cas.org/infopolicy.html

=> d que
L4 STR



Structure attributes must be viewed using STN Express query preparation.
L5 STR



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Structure attributes must be viewed using STN Express query preparation.
L6 109 SEA FILE=REGISTRY SSS FUL L4
L7 22 SEA FILE=REGISTRY SSS FUL L5
L8 26 SEA FILE=CAPLUS L6 AND L7

=> d l8 1-26 ibib abs hitstr

L8 ANSWER 1 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:1091018 CAPLUS
TITLE: Combination therapy formulations comprising thiazolidinedione analogues, glucocorticoid agonist, and nonsteroidal antiinflammatory drugs for treating inflammatory disease
INVENTOR(S): Colca, Gerald R.; Kletzien, Rolf F.
PATENT ASSIGNEE(S): Metabolic Solutions Development Company, USA
SOURCE: PCT Int. Appl., 48pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007109088	A2	20070927	WO 2007-US6508	20070314

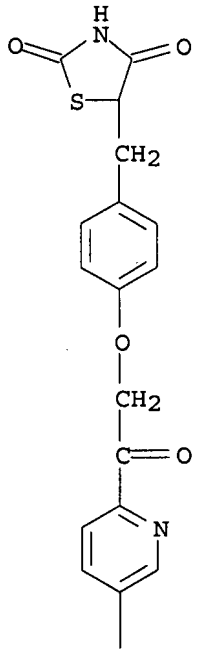
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2006-782972P P 20060316
AB The present invention relates to thiazolidinedione analogs that are useful for treating inflammatory disease. In general, the invention relates to pharmaceutical compns. comprising a combination of glucocorticoid agonists and insulin sensitizers that have reduced activation of the nuclear transcription factor PPARγ. Thus, pharmaceutical composition including a thiazolidinedione analogs can be produced by tableting between 1 mg to 200 mg thiazolidinedione analog, CM-cellulose or carmellose, magnesium stearate, hydroxypropyl cellulose, and lactose monohydrate.
IT 146062-49-9 950696-94-3 950696-95-4
950696-96-5 950696-97-6 950696-98-7

950696-99-8 950697-00-4 950697-01-5
950697-03-7 950697-05-9 950697-07-1
950697-09-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy formulations comprising thiazolidinedione analogs, glucocorticoid agonist, and nonsteroidal antiinflammatory drugs for treating inflammatory disease)

RN 146062-49-9 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)-2-oxoethoxy]phenyl]methyl]- (CA INDEX NAME)

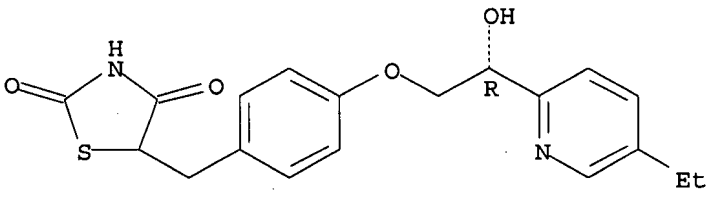
PAGE 1-A



PAGE 2-A

RN 950696-94-3 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[(2R)-2-(5-ethyl-2-pyridinyl)-2-hydroxyethoxy]phenyl]methyl]- (CA INDEX NAME)

Absolute stereochemistry.



RN 950696-95-4 CAPLUS

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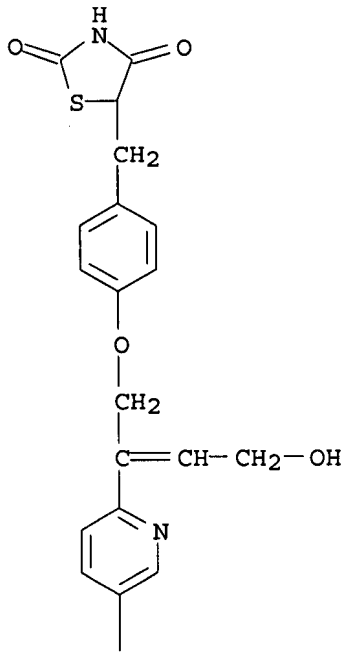


PAGE 2-A

L8 ANSWER 2 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:1090689 CAPLUS
TITLE: Thiazolidinedione analogues for treating hypertension
INVENTOR(S): Colca, Gerard R.; Kletzien, Rolf F.
PATENT ASSIGNEE(S): Metabolic Solutions Development Company, USA
SOURCE: PCT Int. Appl., 57pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007109037	A2	20070927	WO 2007-US6385	20070314

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,

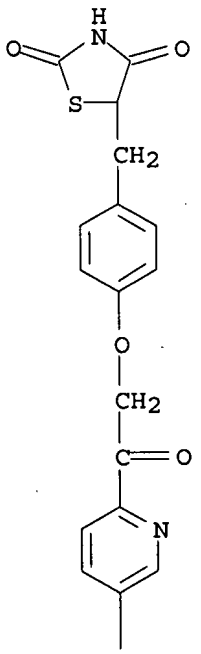
BY, KG, KZ, MD, RU, TJ, TM
PRIORITY APPLN. INFO.: US 2006-782787P P 20060316

AB The present invention relates to thiazolidinedione analogs that are useful for treating hypertension. Thus, pharmaceutical antihypertensive composition comprising a thiazolidinedione analog (15-60 mg), and CM-cellulose, magnesium stearate, hydroxypropyl cellulose, and lactose monohydrate was formulated.

IT 146062-49-9 950696-94-3 950696-95-4
950696-96-5 950696-97-6 950696-98-7
950696-99-8 950697-00-4 950697-01-5
950697-03-7 950697-05-9 950697-07-1
950697-09-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thiazolidinedione analogs for treating hypertension)

RN 146062-49-9 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)-2-oxoethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A



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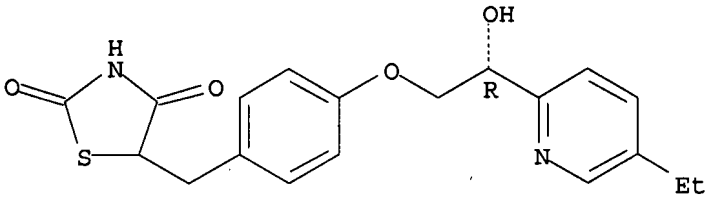
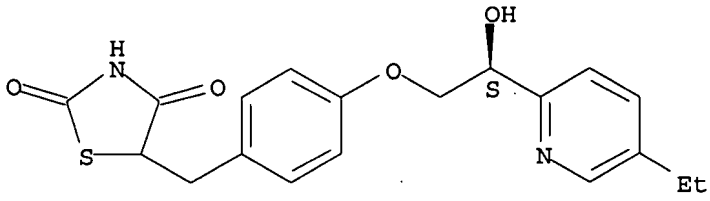
RN 950696-94-3 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[(2R)-2-(5-ethyl-2-pyridinyl)-2-hydroxyethoxy]phenyl]methyl]- (CA INDEX NAME)

Absolute stereochemistry.



RN 950696-95-4 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[(2S)-2-(5-ethyl-2-pyridinyl)-2-hydroxyethoxy]phenyl]methyl]- (CA INDEX NAME)

Absolute stereochemistry.



RN 950696-96-5 CAPLUS
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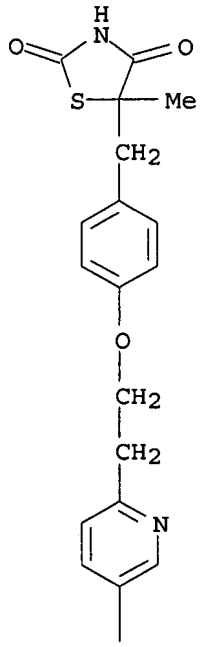
PAGE 1-A



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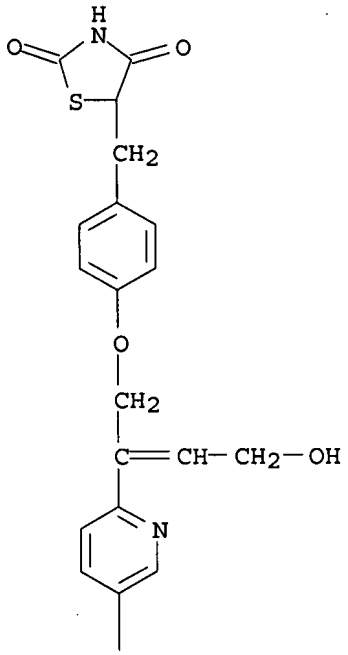

PAGE 2-A

Et

L8 ANSWER 3 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:1090461 CAPLUS
TITLE: Thiazolidinedione analogues for treating metabolic inflammation mediated diseases such as diabetes
INVENTOR(S): Colca, Gerard R.; Kletzien, Rolf F.
PATENT ASSIGNEE(S): Metabolic Solutions Development Company, USA
SOURCE: PCT Int. Appl., 45pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007109024	A2	20070927	WO 2007-US6321	20070314

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GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2006-782894P P 20060316

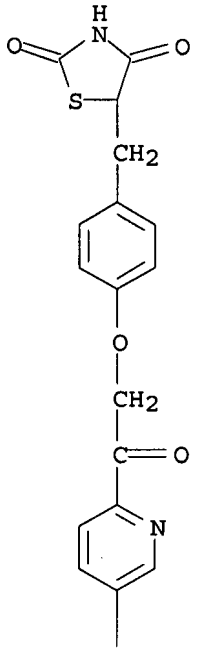
AB The present invention relates to thiazolidinedione analogs that are useful for treating metabolic inflammation mediated diseases such as diabetes. Thus, pharmaceutical composition comprising a thiazolidinedione analog (15-60 mg), and CM-cellulose, magnesium stearate, hydroxypropyl cellulose, and lactose monohydrate was formulated. It exhibited enhanced binding to PPARγ receptors and decreased the glucose, insulin, and triglyceride level in diabetic mice.

IT 146062-49-9 950696-94-3 950696-95-4
950696-96-5 950696-97-6 950696-98-7
950696-99-8 950697-00-4 950697-01-5
950697-03-7 950697-05-9 950697-07-1
950697-09-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thiazolidinedione analogs for treating metabolic inflammation mediated diseases such as diabetes)

RN 146062-49-9 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)-2-oxoethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A



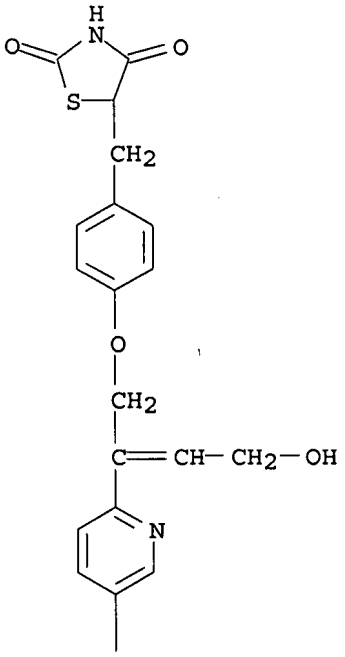
PAGE 2-A

Et

RN 950696-94-3 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[(2R)-2-(5-ethyl-2-pyridinyl)-2-hydroxyethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

L8 ANSWER 4 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1253003 CAPLUS
DOCUMENT NUMBER: 146:804
TITLE: insulin sensitization for delaying puberty and increasing growth
INVENTOR(S): De Zegher, Francis; Dunger, David; Ibanez, Lourdes
PATENT ASSIGNEE(S): K.U. Leuven Research and Development, Belg.; Addenbrooke's Hospital
SOURCE: PCT Int. Appl., 61pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006125285	A1	20061130	WO 2006-BE60	20060523
WO 2006125285	B1	20070111		

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RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: GB 2005-10469 A 20050523

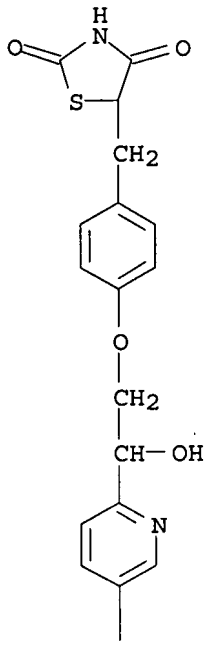
OTHER SOURCE(S): MARPAT 146:804

AB In accordance with the purpose of the invention, as embodied and broadly described herein, the invention is broadly drawn to a new method of treatment, the use of agents to manufacture a composition of treatment or the composition of treatment for the prevention of rapidly progressive puberty, the prevention of early menarche or the modulation, more particularly the delay, of the tempo of puberty in a female mammal, preferably a human girl, and the disorders related thereto. In a particular embodiment the present invention involves the use of at least one insulin-sensitizing agent such as metformin, any of the polymorphs of metformin or a pharmaceutically acceptable salt thereof for the preparation of a composition of treatment to modulate the tempo of pubertal progression in a girl. Metformin administration to girls experiencing precocious puberty resulted in normalization of pubertal progression to menarche, increased height gains, leaner body composition, and decreases indexes relating to insulin resistance.

IT 101931-00-4 105355-33-7 111025-46-8, Pioglitazone 146062-44-4 146062-45-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(metformin-induced insulin sensitization for delaying puberty and increasing growth)

RN 101931-00-4 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)-2-hydroxyethoxy]phenyl]methyl]- (CA INDEX NAME)



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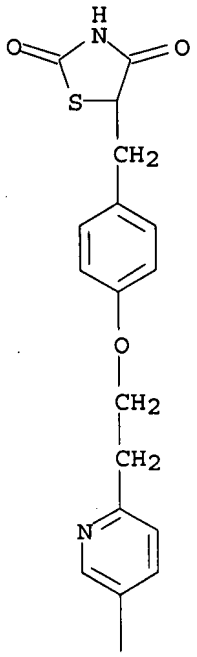


PAGE 2-A

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:799525 CAPLUS
DOCUMENT NUMBER: 145:305561
TITLE: Pioglitazone is metabolised by CYP2C8 and CYP3A4 in vitro: potential for interactions with CYP2C8 inhibitors
AUTHOR(S): Jaakkola, Tiina; Laitila, Jouko; Neuvonen, Pertti J.; Backman, Janne T.
CORPORATE SOURCE: Department of Clinical Pharmacology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland
SOURCE: Basic & Clinical Pharmacology & Toxicology (2006), 99(1), 44-51
CODEN: BCPTBO; ISSN: 1742-7835
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Our objective was to identify the cytochrome P 450 (CYP) enzymes that metabolize pioglitazone and to examine the effects of the CYP2C8 inhibitors montelukast, zafirlukast, trimethoprim and gemfibrozil on pioglitazone metabolism in vitro. The effect of different CYP isoform inhibitors on the elimination of a clin. relevant concentration of pioglitazone (1 μM) and the formation of the main primary metabolite M-IV were studied using pooled human liver microsomes. The metabolism of pioglitazone

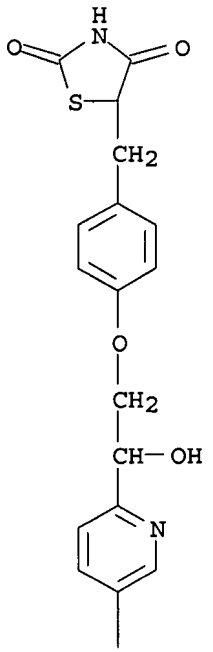
by CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP3A5 was investigated using human recombinant CYP isoforms. In particular, the inhibitors of CYP2C8, but also those of CYP3A4, markedly inhibited the elimination of pioglitazone and the formation of M-IV by HLM. Inhibitors selective to other CYP isoforms had a minor effect only. Of the recombinant isoforms, CYP2C8 (20 pmol/mL) metabolized pioglitazone markedly (56% in 60 min.), and also CYP3A4 had a significant effect (37% in 60 min.). Montelukast, zafirlukast, trimethoprim and gemfibrozil inhibited pioglitazone elimination in HLM with IC50 values of 0.51 μM, 1.0 μM, 99 μM and 98 μM, resp., and the formation of the metabolite M-IV with IC50 values of 0.18 μM, 0.78 μM, 71 μM and 59 μM, resp. In conclusion, pioglitazone is metabolized mainly by CYP2C8 and to a lesser extent by CYP3A4 in vitro. CYP2C9 is not significantly involved in the elimination of pioglitazone. The effect of different CYP2C8 inhibitors on pioglitazone pharmacokinetics needs to be evaluated also in vivo because, irresp. of their in vitro CYP2C8 inhibitory potency, their pharmacokinetic properties may affect the extent of interaction.

IT 176109-96-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pioglitazone is metabolized by CYP2C8 and CYP3A4 in vitro: potential for interactions with CYP2C8 inhibitors)

RN 176109-96-9 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-hydroxy-2-[5-(1-hydroxyethyl)-2-pyridinyl]ethoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



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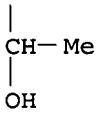
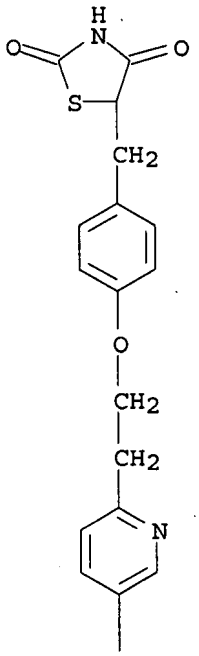


IT 111025-46-8, Pioglitazone
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(pioglitazone is metabolized by CYP2C8 and CYP3A4 in vitro: potential for interactions with CYP2C8 inhibitors)
RN 111025-46-8 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

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REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:370121 CAPLUS
DOCUMENT NUMBER: 145:240842
TITLE: Simultaneous determination of pioglitazone and its two active metabolites in human plasma by HPLC-MS
AUTHOR(S): Deng, Lijing; Wang, Feng; Xie, Zhihong; Xiao, Yiwen; Li, Huande
CORPORATE SOURCE: Second Xiangya Hospital, Central-South University, Changsha, Hunan Province, 410011, Peop. Rep. China
SOURCE: Zhongguo Yaoxue Zazhi (Beijing, China) (2005), 40(10), 772-774
CODEN: ZYZAEU; ISSN: 1001-2494
PUBLISHER: Zhongguo Yaoxue Zazhishe
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

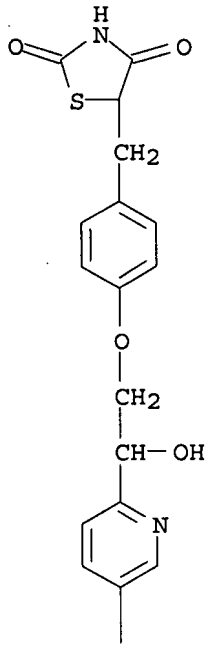
AB A HPLC-MS method was established for simultaneous determining of pioglitazone and its two active metabolites: M-III (keto-derivative) and M-IV (hydroxy-derivative) in human plasma. The separation was performed on a Waters XTerraTM C18 column (2.1 mm+150 mm, 3.5 μm) with guard column Phenomenex C18. The column temperature was 50 degree. The mobile phase consisted of acetonitrile-30 mmol·L-1 ammonium acetate solution (added with 0.1% formic acid and 0.05% trifluoroacetic acid) (35:65), with a flow rate of 0.22 mL·min-1. The compound was ionized in the electrospray ionization (ESI) ion source of the mass spectrometer and selected ion mass spectral (m/z) 357.4 (PIO), 358.2 (is), 371.5 (M-III), 373.2 (M-IV) to quantify. Human plasma samples were extracted with 1:2 chlorform:methyl t-Bu ether after acidification. The linear ranges were 11.16-1748.60 ng·mL-1 for pioglitazone, 3.33-520.50 ng·mL-1 for M-III and 5.00-687.50 ng·mL-1 for M-IV (r≥0.9997), and their detect limits were 2.90, 1.10, 1.20 ng·mL-1. Recoveries were within 90%-110%, and intra-and inter-day RSDs were all less than 15%. The method is found to be sensitive, rapid and accurate, and has been applied successfully to sample anal. for clin. study of pioglitazone pharmacokinetics and drug interaction.

IT 101931-00-4 146062-45-5
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(simultaneous determination of pioglitazone and its two active metabolites in
human plasma by HPLC-MS)

RN 101931-00-4 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)-2-hydroxyethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A



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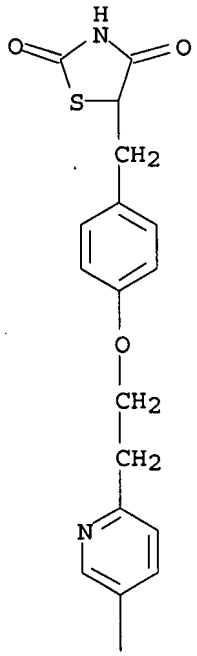
RN 146062-45-5 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-acetyl-2-pyridinyl)ethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A

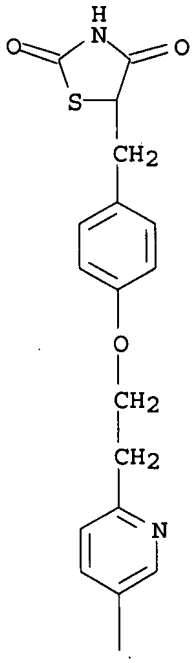


PAGE 2-A

IT 111025-46-8, Pioglitazone
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(simultaneous determination of pioglitazone and its two active metabolites in human plasma by HPLC-MS)

RN 111025-46-8 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

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L8 ANSWER 7 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:72865 CAPLUS
DOCUMENT NUMBER: 145:20356
TITLE: Effect of rifampicin on the pharmacokinetics of pioglitazone
AUTHOR(S): Jaakkola, Tiina; Backman, Janne T.; Neuvonen, Mikko; Laitila, Jouko; Neuvonen, Pertti J.
CORPORATE SOURCE: Department of Clinical Pharmacology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland
SOURCE: British Journal of Clinical Pharmacology (2006), 61(1), 70-78
CODEN: BCPHBM; ISSN: 0306-5251
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Aims The effect of enzyme induction on the pharmacokinetics of pioglitazone, a thiazolidinedione antidiabetic drug that is metabolized primarily by CYP2C8, is not known. Rifampicin is a potent inducer of several CYP enzymes and our objective was to study its effects on the pharmacokinetics of pioglitazone in humans. Methods In a randomized, two-phase crossover study, ten healthy subjects ingested either 600 mg rifampicin or placebo once daily for 6 days. On the last day, they received a single oral dose of 30 mg pioglitazone. The plasma concns. and cumulative excretion of pioglitazone and its active metabolites M-IV and M-III into urine were measured up to 48 h. Results Rifampicin decreased

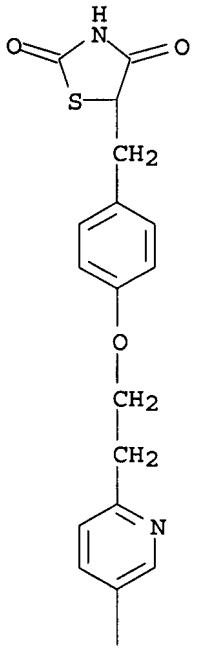
the mean total area under the plasma concentration-time curve (AUC0-∞) of pioglitazone by 54% (range 20-66%; P = 0.0007; 95% confidence interval -78 to -30%) and shortened its dominant elimination half-life (t1/2) from 4.9 to 2.3 h (P = 0.0002). No significant effect on peak concentration (Cmax) or time to peak (tmax) was observed Rifampicin increased the apparent formation rate of M-IV and shortened its tmax (P < 0.01). It also decreased the AUC0-∞ of M-IV (by 34%; P = 0.0055) and M-III (by 39%; P = 0.0026), shortened their t1/2 (M-IV by 50%; P = 0.0008, and M-III by 55%; P = 0.0016) and increased the AUC0-∞ ratios of M-IV and M-III to pioglitazone by 44% (P = 0.0011) and 32% (P = 0.0027), resp. Rifampicin increased the M-IV/pioglitazone and M-III/pioglitazone ratios in urine by 98% (P = 0.0015) and 95% (P = 0.0024). A previously unrecognized metabolite M-XI, tentatively identified as a dihydroxy metabolite, was detected in urine during both phases, and rifampicin increased the ratio of M-XI to pioglitazone by 240% (P = 0.0020). Conclusions Rifampicin caused a substantial decrease in the plasma concentration of pioglitazone, probably by induction of CYP2C8. Concomitant use of rifampicin with pioglitazone may decrease the efficacy of the latter drug.

IT 111025-46-8, Pioglitazone
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rifampicin decreased AUC, t1/2 of pioglitazone and its metabolites M-III, M-IV, did not affect Cmax, tmax of pioglitazone, increased Kf of M-IV, increased M-IV/pioglitazone, M-III/pioglitazone ratios in healthy human)

RN 111025-46-8 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A



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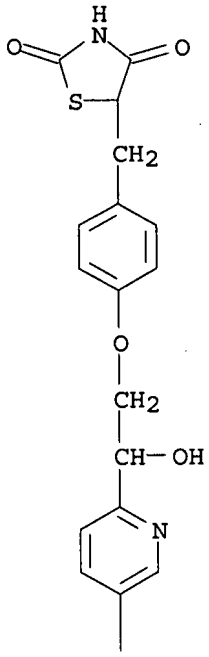
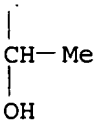


PAGE 2-A



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

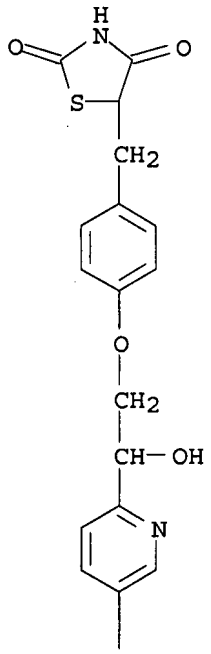
L8 ANSWER 8 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:1259919 CAPLUS
DOCUMENT NUMBER: 144:324098
TITLE: Effect of gemfibrozil on the pharmacokinetics of pioglitazone
AUTHOR(S): Deng, Li-Jing; Wang, Feng; Li, Huan-De
CORPORATE SOURCE: Clinical Pharmaceutical Research Institute, The Second Xiangya Hospital, The Central South University, Changsha, 410011, Peop. Rep. China
SOURCE: European Journal of Clinical Pharmacology (2005), 61(11), 831-836
CODEN: EJCPAS; ISSN: 0031-6970
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: Our objective was to study the effects of gemfibrozil on the pharmacokinetics of pioglitazone and the active compds., which are all the substrates of CYP2C8 and CYP3A4. Methods: In a randomized, two-phase crossover study, 10 healthy volunteers were pretreated for 2 days with either 600 mg oral gemfibrozil or placebo twice daily. On day 3, they received a single dose of 600 mg gemfibrozil or placebo, and 1 h later they received a single oral dose of 30 mg pioglitazone. Plasma concns. of

pioglitazone and both active metabolites M-III and M-IV were measured for up to 120 h. Results: Gemfibrozil raised the mean total area under the concentration-time curve (AUC) of parent pioglitazone 3.4-fold (P<0.001). No statistically significant changes were seen in the total AUC of M-III or M-IV after gemfibrozil pretreatment. Gemfibrozil reduced the M-III/pioglitazone and M-IV/pioglitazone AUC0-∞ ratio by 71% (P<0.001) and 65%(P<0.001), strikingly prolonging their t1/2. Conclusion: Gemfibrozil greatly increased the plasma concentration of parent pioglitazone and also inhibited the further metabolism of M-III and M-IV. Careful blood glucose monitoring and dosage adjustments are suggested during coadministration of pioglitazone and gemfibrozil.

IT 101931-00-4 146062-45-5
RL: BSU (Biological study, unclassified); PKT (Pharmacokinetics); BIOL (Biological study)
(gemfibrozil inhibited metabolism of pioglitazone metabolite M-III and M-IV showing that careful blood glucose monitoring and dosage adjustment are required during their coadministration in human)

RN 101931-00-4 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)-2-hydroxyethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A



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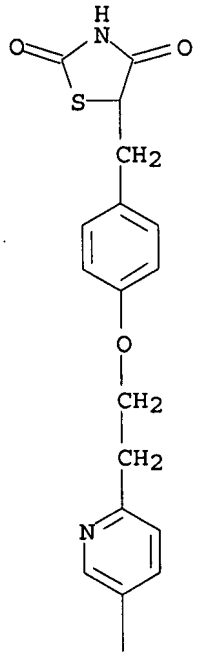
RN 146062-45-5 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-acetyl-2-pyridinyl)ethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A



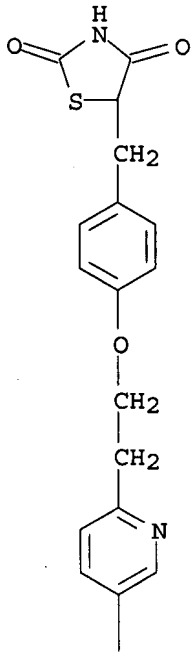
PAGE 2-A

IT 111025-46-8, Pioglitazone
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gemfibrozil markedly increased pioglitazone plasma concentration while inhibited M-III and M-IV metabolism showing that careful blood glucose monitoring and dosage adjustment are required during their coadministration in human)

RN 111025-46-8 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 9 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:1139098 CAPLUS
DOCUMENT NUMBER: 144:141941
TITLE: Single- and multiple-dose pharmacokinetics of pioglitazone in adolescents with type 2 diabetes
AUTHOR(S): Christensen, Michael L.; Meibohm, Bernd; Capparelli, Edmund V.; Velasquez-Mieyer, Pedro; Burghen, George A.; Tamborlane, William V.
CORPORATE SOURCE: Pediatric Pharmacology Research Units, The University of Tennessee and LeBonheur Children's Medical Center, Memphis, USA
SOURCE: Journal of Clinical Pharmacology (2005), 45(10), 1137-1144
CODEN: JCPCBR; ISSN: 0091-2700
PUBLISHER: Sage Publications
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study assessed the single- and multiple-dose pharmacokinetics of 3 doses (15 mg, 30 mg, and 45 mg) of pioglitazone in 36 adolescents with type 2 diabetes. Blood samples were obtained over a 48-h interval after the first dose (day 1) and over a 72-h interval after the last dose (day 15) of pioglitazone and were assayed for pioglitazone and active metabolites (M-III and M-IV). Pioglitazone systemic exposure increased dose dependency but was less than dose proportional during multiple

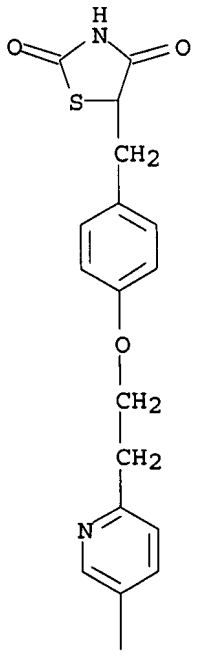
dosing. The median peak pioglitazone concentration occurred at 2 h. The mean half-life was 8 to 9 h for pioglitazone and 24 to 32 h for M-III and M-IV, with similar values at each dose level. During multiple dosing, accumulation for pioglitazone was negligible, but it reached 2.5- to 3.0-fold for M-III and M-IV. The sustained total serum concentration of active compds. during multiple dosing provides the basis for once-daily dose administration of pioglitazone in adolescents.

IT 146062-45-5
RL: BSU (Biological study, unclassified); PKT (Pharmacokinetics); BIOL (Biological study)
(pharmacokinetic anal. of pioglitazone metabolite M-III revealed less dose-proportional increase in Cmax and AUC during multiple dosing compared to single dosing in adolescent with type 2 diabetes)

RN 146062-45-5 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-acetyl-2-pyridinyl)ethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

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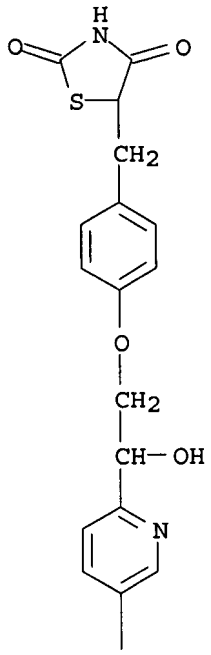
IT 101931-00-4
RL: BSU (Biological study, unclassified); PKT (Pharmacokinetics); BIOL (Biological study)
(pharmacokinetic anal. of pioglitazone metabolite M-IV revealed less dose-proportional increase in Cmax and AUC during multiple dosing compared to single dosing in adolescent with type 2 diabetes)

RN 101931-00-4 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)-2-hydroxyethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

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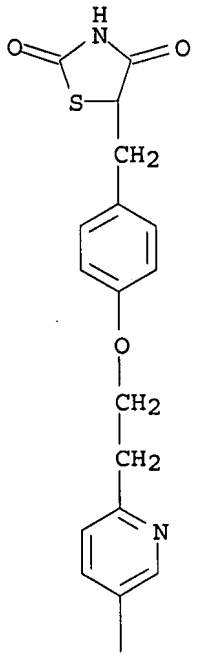
IT 111025-46-8, Pioglitazone
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacokinetic anal. of pioglitazone revealed less dose-proportional increase in Cmax and AUC during multiple dosing compared to single dosing in adolescent with type 2 diabetes)

RN 111025-46-8 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 10 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:60504 CAPLUS
DOCUMENT NUMBER: 140:111409
TITLE: A novel process to prepare pioglitazone via several novel intermediates.
INVENTOR(S): Pandey, Bipin; Lohray, Vidya Bhushan; Lohray, Braj Bhushan
PATENT ASSIGNEE(S): Cadila Healthcare Limited, India
SOURCE: PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004007490	A2	20040122	WO 2003-IN241	20030715
WO 2004007490	A3	20040325		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,

TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

IN	2002MU00648	A	20040424	IN 2002-MU648	20020716
AU	2003272072	A1	20040202	AU 2003-272072	20030715
EP	1521753	A2	20050413	EP 2003-753913	20030715
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AT	372336	T	20070915	AT 2003-753913	20030715
US	2006167061	A1	20060727	US 2005-520166	20051004

PRIORITY APPLN. INFO.: IN 2002-MU648 A 20020716
WO 2003-IN241 W 20030715

OTHER SOURCE(S): CASREACT 140:111409; MARPAT 140:111409

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention discloses a novel and general process to prepare various pyridine substituted 5-[4-[2-(alkyl substituted pyridyl)ethoxy]benzyl]-2,4-thiazolidinone derivs. of general formula I [R = alkyl], and their pharmaceutically acceptable salts. The present invention especially provides a novel process to prepare pioglitazone hydrochloride [R = 5-ethyl], via novel intermediates, i.e. II and III. This process involves lesser number of steps with high yields and uses key solid intermediates, which are operationally simple, and therefore offers opportunities for better com. viability.

IT 101931-00-4P 111025-46-8P 646519-87-1P
646519-88-2P 646519-89-3P 646519-91-7P
646519-93-9P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of pioglitazone via several novel intermediates)

RN 101931-00-4 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)-2-hydroxyethoxy]phenyl]methyl]- (CA INDEX NAME)

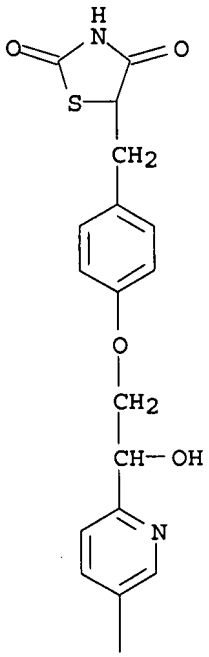
L8 ANSWER 11 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:766616 CAPLUS
DOCUMENT NUMBER: 140:192140
TITLE: Sex differences in the pharmacokinetics of Pioglitazone in rats
AUTHOR(S): Fujita, Yukiyoshi; Yamada, Yasuhiko; Kusama, Makiko; Yamauchi, Toshimasa; Kamon, Junji; Kadowaki, Takashi; Iga, Tatsuji
CORPORATE SOURCE: Faculty of Medicine, University of Tokyo Hospital, Department of Pharmacy, University of Tokyo, Bunkyo-ku, Tokyo, Japan
SOURCE: Comparative Biochemistry and Physiology, Part C: Toxicology & Pharmacology (2003), 136C(1), 85-94
CODEN: CBPPFK; ISSN: 1532-0456
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Clin. studies have suggested that Pioglitazone, an insulin sensitizer, has a stronger effect in women than in men. To determine the sex difference in the pharmacokinetics of Pioglitazone, the authors examined the plasma and white adipose tissue levels of Pioglitazone and its active metabolites (M-II, M-III, and M-IV) in male and female rats treated with a single or repeated oral administration of Pioglitazone (10 mg/kg). The AUCs of Pioglitazone (149.6±22.6 vs. 103.3±14.0 μg·h/mL; P<0.01), M-III (31.4±8.1 vs. 20.2±4.7 μg·h/mL; P<0.05), and M-IV (41.9±15.5 vs. 14.1±1.6 μg·h/mL; P<0.01) were larger in female rats than in male rats, but the levels of M-II were similar. Any of the compds. did not accumulate in plasma after repeated administration. According to kinetic model anal., the apparent elimination rate of Pioglitazone and the formation rate of M-II were faster in male rats than in female rats. No significant sex difference was found in the tissue-to-plasma concentration ratios of Pioglitazone or its active metabolites in white adipose tissue. These results suggest that there are sex differences in the plasma levels of Pioglitazone and some of its active metabolites and that those differences are reflected in differences in white adipose tissue levels.

IT 101931-00-4 111025-46-8D, Pioglitazone, metabolites
146062-44-4 146062-45-5
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(Pioglitazone and its active metabolites in blood plasma and white adipose tissue of male and female rats after oral administration of Pioglitazone)

RN 101931-00-4 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)-2-hydroxyethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A

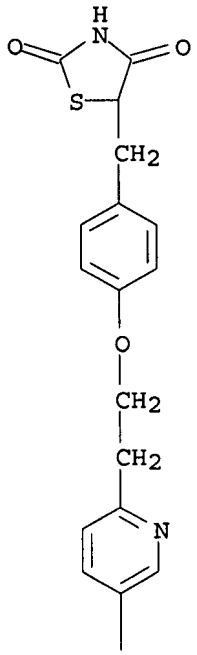


PAGE 2-A

Et

RN 111025-46-8 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-
(CA INDEX NAME)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

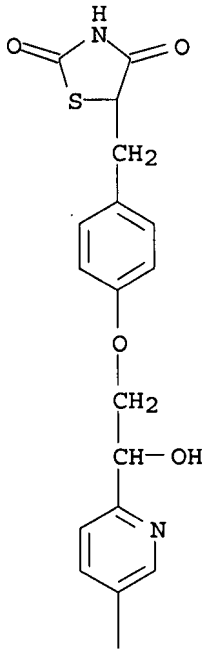
L8 ANSWER 12 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:389760 CAPLUS
DOCUMENT NUMBER: 140:238
TITLE: Identification of novel metabolites of pioglitazone in rat and dog
AUTHOR(S): Shen, Z.; Reed, J. R.; Creighton, M.; Liu, D. Q.; Tang, Y. S.; Hora, D. F.; Feeney, W.; Szewczyk, J.; Bakhtiar, R.; Franklin, R. B.; Vincent, S. H.
CORPORATE SOURCE: Departments of Drug Metabolism, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Xenobiotica (2003), 33(5), 499-509
CODEN: XENOBH; ISSN: 0049-8254
PUBLISHER: Taylor & Francis Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Four new metabolites of pioglitazone were identified by liquid chromatog.-mass spectrometry (LC-MS/MS) as being formed by hydroxylation (M-VII and M-VIII), opening of the thiazolidinedione ring (M-X) and by desatn. of the terminal Et side chain or tether ethoxy moiety (M-IX), resp. The structure of one of the hydroxylated metabolites (M-VII) was confirmed by chemical modification using the Jones reaction. Oxidative cleavage of the thiazolidinedione ring is a novel pathway not previously reported for pioglitazone. The hydroxylated M-VII was detected in incubations with rat, dog and human liver and kidney microsomes, and in

plasma from rats and dogs dosed orally with [3H]pioglitazone. The carboxylic acid derivative of M-VII (M-V) and its taurine conjugate were the major radioactive components in dog bile.

IT 101931-00-4 146062-44-4 146062-45-5
146062-48-8 157142-91-1 186751-40-6
625853-75-0 625853-76-1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Identification and localization of novel metabolites of pioglitazone in rat and dog)

RN 101931-00-4 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)-2-hydroxyethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

Et

RN 146062-44-4 CAPLUS
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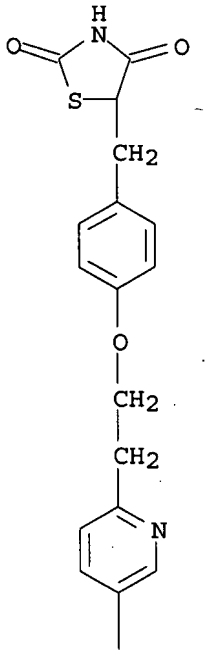
PAGE 1-A



PAGE 2-A

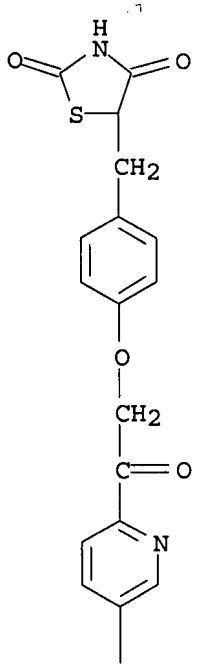
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 13 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:610859 CAPLUS
DOCUMENT NUMBER: 137:312674
TITLE: Process Development and Scale-Up of the Potential Thiazolidinedione Antidiabetic Candidate PNU-91325
AUTHOR(S): Carpenter, Donald E.; Imbordino, Rick J.; Maloney, Mark T.; Moeslein, Jeffery A.; Reeder, Michael R.; Scott, Allen
CORPORATE SOURCE: Early Process Research and Development, Pharmacia Corporation, Kalamazoo, MI, 49001, USA
SOURCE: Organic Process Research & Development (2002), 6(5), 721-728
CODEN: OPRDFK; ISSN: 1083-6160
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An efficient six-step synthesis was developed for the preparation of the thiazolidinedione analog PNU-91325 from a com. available olefin. This process involves a novel epoxide ring opening with a deactivated phenol under phase-transfer conditions. Significant improvements were made in the oxidation of a secondary alc. to the ketone and the 1,4-reduction of an enone from a previous process. Overall, this route allows for the preparation of PNU-91325 in 25% yield.

IT 146062-49-9P
RL: IMF (Industrial manufacture); PREP (Preparation)
(potential antidiabetic agent; process development and scale-up of potential thiazolidinedione antidiabetic candidate PNU-91325)
RN 146062-49-9 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)-2-oxoethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A

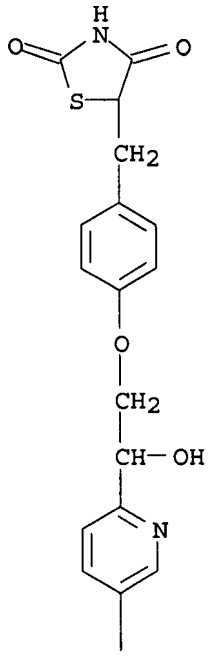


PAGE 2-A

Et

IT 101931-00-4P
RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(process development and scale-up of potential thiazolidinedione antidiabetic candidate PNU-91325)
RN 101931-00-4 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)-2-hydroxyethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 14 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:753074 CAPLUS
DOCUMENT NUMBER: 131:346538
TITLE: Thiazolidine and oxazolidine derivatives for the treatment of acute myocardial infarction and inhibition of cardiomyocyte apoptosis
INVENTOR(S): Wang, Ping H.
PATENT ASSIGNEE(S): Regents of the University of California, USA
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9959586	A1	19991125	WO 1999-US11101	19990519

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9940052	A	19991206	AU 1999-40052		19990519
PRIORITY APPLN. INFO.:			US 1998-86030P	P	19980519
			US 1998-87204P	P	19980528
			WO 1999-US11101	W	19990519

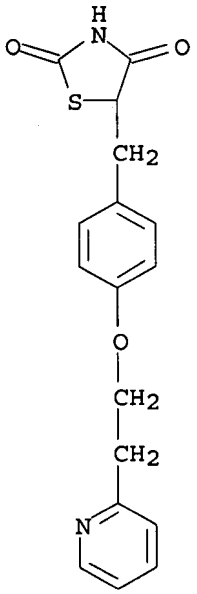
OTHER SOURCE(S): MARPAT 131:346538

AB It has been demonstrated that antidiabetic thiazolidine and oxazolidine derivs. (glitazones) exhibit novel effects on apoptosis of cardiomyocytes. These substances are capable of greatly decreasing apoptosis by a pathway that is not Caspase 3 dependent. Addition of IGF1 to the treatment further prevents apoptosis. Glitazones alone or glitazones plus IGF1 should be administered at the beginning of a myocardial infarction and continued through the recuperation period to reduce morbidity and prevent unfavorable remodeling of the myocardium. Thus, troglitazone (5 μM), when added to a culture medium, reduced doxorubicin-induced apoptosis of cardiomyocyte by approx. 60%.

IT 74773-17-4 101930-98-7 101931-00-4
111025-46-8, Pioglitazone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thiazolidine and oxazolidine derivs. for treatment of acute myocardial infarction and inhibition of cardiomyocyte apoptosis)

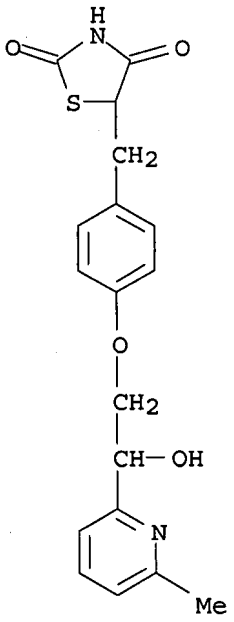
RN 74773-17-4 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-(2-pyridinyl)ethoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



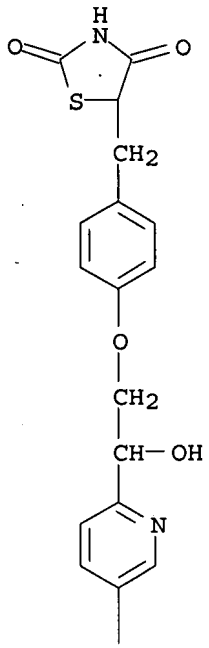
RN 101930-98-7 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-hydroxy-2-(6-methyl-2-pyridinyl)ethoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 101931-00-4 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)-2-hydroxyethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A

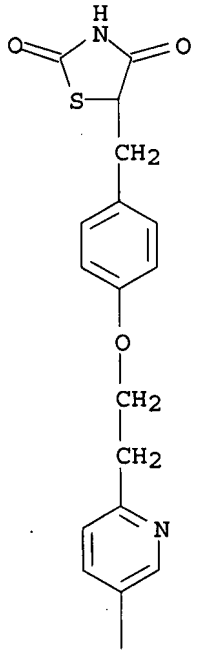


PAGE 2-A

Et

RN 111025-46-8 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

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REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

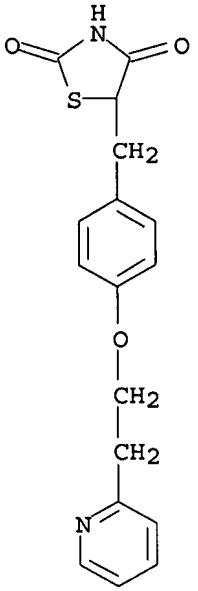
L8 ANSWER 15 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:485977 CAPLUS
DOCUMENT NUMBER: 131:252097
TITLE: Three-dimensional quantitative structure activity relationships (3-D-QSAR) of antihyperglycemic agents
AUTHOR(S): Kulkarni, Santosh S.; Gediya, Lalji K.; Kulkarni, Vithal M.
CORPORATE SOURCE: Pharmaceutical Division, Department of Chemical Technology, University of Mumbai, Mumbai, 400 019, India
SOURCE: Bioorganic & Medicinal Chemistry (1999), 7(7), 1475-1485
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal
LANGUAGE: English

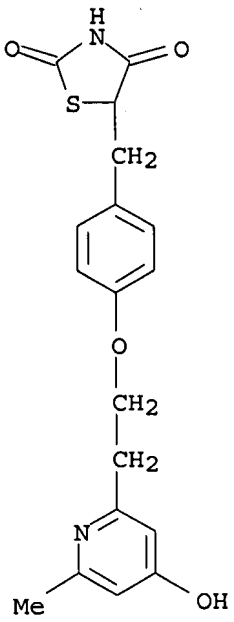
AB A three-dimensional quant. structure activity relationship study (3-D-QSAR) was performed on a set of thiazolidinedione antihyperglycemic agents using the comparative mol. field anal. (CoMFA) method. The CoMFA models were derived from a training set of 53 compds. Fifteen compds., which were not used in model generation were used to validate the CoMFA models. All the compds. were superimposed to the template structure by atom-based and shape-based strategies. The SYBYL QSAR rigid body field fit was also used for aligning the ligands. A total of twelve different alignments were generated. The resulting models exhibited a good cross-validated rcv2 values (0.624-0.764) and the conventional r2 values (0.689-0.921). A more robust cross-validation test using cross-validation by 2 groups (leave half out method) was performed 100 times to ascertain the predictiveness of the CoMFA models. The mean of rcv2 values from 100 runs ranged from 0.611-0.690. Few models exhibited good external predictivity. These models were then used to define a hypothetical receptor model for antihyperglycemic agents.

IT 74773-17-4 74773-19-6 101930-98-7
101930-99-8 101931-00-4 101931-04-8
101931-05-9 101946-34-3 101946-35-4
105355-33-7 105355-34-8 105355-35-9
111025-46-8 127676-13-5 127676-14-6
127676-15-7
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(3-D-QSAR of antihyperglycemic agents)

RN 74773-17-4 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(2-pyridinyl)ethoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



RN 74773-19-6 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(6-methyl-2-pyridinyl)ethoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 16 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:93456 CAPLUS
DOCUMENT NUMBER: 126:287573
TITLE: Disposition of the new antidiabetic agent pioglitazone in rats, dogs, and monkeys
AUTHOR(S): Maeshiba, Yoshihiro; Kiyota, Yutaka; Yamashita, Kenji; Yoshimura, Yoshinobu; Motohashi, Michio; Tanayama, Shigeharu
CORPORATE SOURCE: Drug Analysis Pharmacokinetics Research Laboratories, Takeda Chemical Industries Ltd., Osaka, 532, Japan
SOURCE: Arzneimittel-Fórschung (1997), 47(1), 29-35
CODEN: ARZNAD; ISSN: 0004-4172
PUBLISHER: Cantor
DOCUMENT TYPE: Journal
LANGUAGE: English

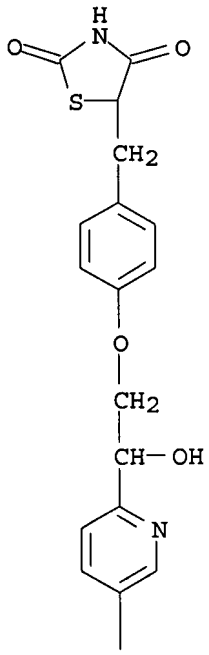
AB The disposition of pioglitazone was studied after oral administration to rats, dogs, and monkeys using 14C-labeled drug. After oral dosing, pioglitazone was well absorbed from the gastrointestinal tract at an extent of 96, 95, and 90% in rats, dogs, and monkeys, resp. In rats, the concentration of pioglitazone in plasma reached a peak (Cmax 0.71 μg/mL) at 4 h (tmax) after dosing and declined with a half-life (t1/2) of 2.6 h. In dogs, tmax, Cmax and t1/2 were 0.5 h, 0.32 μg/mL and 2.1 h, and those for monkeys were 4.3 h, 0.48 μg/mL and 5.3 h, resp. The drug was metabolized mainly to M-I to M-VI including the pharmacol. active metabolites (M-II, III, and IV). The pharmacol. active compds. (total of the unchanged compound and the above three active metabolites) accounted for 87, 71 and 73% of the radioactivity in plasma of rats, dogs, and monkeys, resp. The radioactivity was widely distributed in tissues after oral administration to rats, and decreased to the very low concentration within 24 to 72 h after dosing. Radioactivity dose was almost completely excreted in urine and feces.

IT 101931-00-4 146062-44-4 146062-45-5
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation,

nonpreparative); PROC (Process)
(disposition of antidiabetic pioglitazone in rats, dogs, and monkeys)

RN 101931-00-4 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)-2-hydroxyethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

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RN 146062-44-4 CAPLUS
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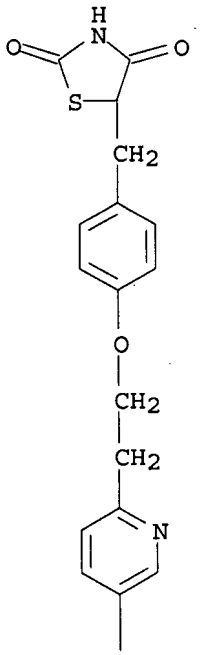
PAGE 1-A



PAGE 2-A

L8 ANSWER 17 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:93455 CAPLUS
DOCUMENT NUMBER: 126:287572
TITLE: Studies on the metabolism of the new antidiabetic agent pioglitazone. Identification of metabolites in rats and dogs
AUTHOR(S): Kiyota, Yutaka; Kondo, Takahiro; Maeshiba, Yoshihiro; Hashimoto, Ai; Yamashita, Kenji; Yoshimura, Yoshinobu; Motohashi, Michio; Tanayama, Shigeharu
CORPORATE SOURCE: Drug Analysis Pharmacokinetics Research Laboratories, Takeda Chemical Industries Ltd., Osaka, 532, Japan
SOURCE: Arzneimittel-Forschung (1997), 47(1), 22-28
CODEN: ARZNAD; ISSN: 0004-4172
PUBLISHER: Cantor
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Metabolic studies of pioglitazone,, a new antidiabetic agent, in rats and dogs using liquid chromatog./tandem mass spectrometry and 1H-NMR led to characterization of the following metabolites: the parent compound, (±)-5-(p-hydroxybenzyl)-2,4-thiazolidinedione (M-I), (±)-5-[p-[2-(5-ethyl-2-pyridyl)-2-hydroxyethoxy]benzyl]-2,4-thiazolidinedione (M-II), (±)-5-[p-[2-(5-acetyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (M-III), (±)-5-[p-[2-[5-(1-hydroxyethyl)-2-pyridyl]ethoxy]benzyl]-2,4-thiazolidinedione (M-IV), (±)-5-[p-[2-(5-carboxymethyl-2-pyridyl)ethoxy]-benzyl]-2,4-thiazolidinedione (M-V), and (±)-5-[p-[2-(5-carboxy-2-

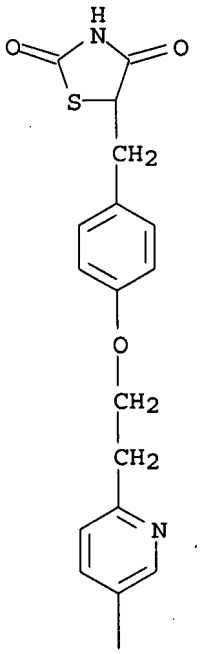
pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (M-VI). Pioglitazone is considered to be metabolized by cleavage of aliphatic C0 bond to lead to M-I, hydroxylation of aliphatic methylene groups to form M-II and M-IV, oxidation of M-IV to give M-III, oxidation of the Et group to form M-V, and oxidative loss of the terminal carbon to lead to M-VI. Furthermore, part of metabolites exist as conjugated form. Among the conjugates, M-IV conjugated with sulfuric acid and M-V conjugated with taurine were identified.

IT 111025-46-8, Pioglitazone
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(metabolism of antidiabetic pioglitazone and identification of metabolites in rats and dogs)

RN 111025-46-8 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

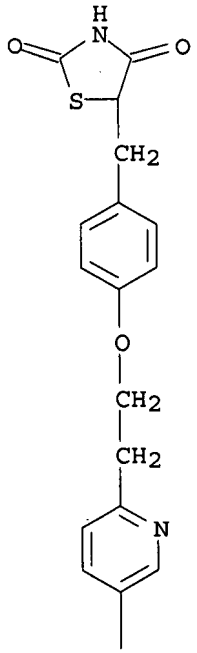
Et

IT 101931-00-4 146062-44-4 146062-45-5
146062-48-8 186751-40-6
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(metabolism of antidiabetic pioglitazone and identification of metabolites in rats and dogs)

RN 101931-00-4 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)-2-hydroxyethoxy]phenyl]methyl]- (CA INDEX NAME)

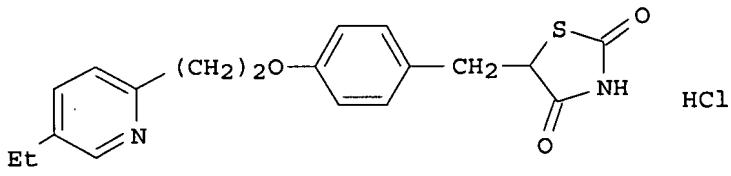
PAGE 1-A



PAGE 2-A

L8 ANSWER 18 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1997:57026 CAPLUS
DOCUMENT NUMBER: 126:152372
TITLE: Disposition of AD-4833, a new antidiabetic agent, in animals
AUTHOR(S): Maeshiba, Yoshihiro; Kiyota, Yutaka; Yamashita, Kenji; Yoshimura, Yoshinobu; Motohashi, Michio; Tanayama, Shigeharu
CORPORATE SOURCE: Drug analysis and Pharmacokinetics Research Laboratories, Takeda Chemical Industries, Ltd., Japan
SOURCE: Yakuri to Chiryo (1996), 24(12), 2597-2617
CODEN: YACHDS; ISSN: 0386-3603
PUBLISHER: Raifu Saiensu Shuppan K.K.
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
GI



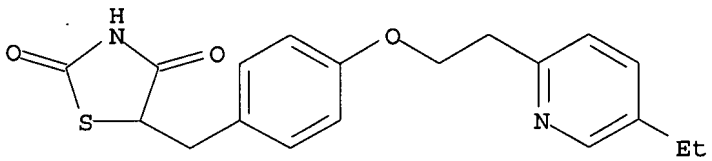
I

AB The disposition of AD-4833 (I) was studied after oral administration to mice, rats, dogs, and monkeys, using [14C]AD-4833-HCl. Concns. of AD-4833 in mouse plasma attained a peak (Cmax, 0.51 μg/mL) 1.0 h (Tmax) after administration and declined with an apparent half-life (t1/2) of 3.1 h. Concns. of AD-4833 in rat plasma attained a peak (Cmax, 0.71 μg/mL) 4.0 h (Tmax) after administration and declined with t1/2 of 2.6 h. Tmax, Cmax, and t1/2 in dogs were 0.5 h, 0.32 μg/mL, and 2.1 h, resp., and those in monkeys were 4.3 h, 0.48 μg/mL, and 5.3 h, resp. The bioavailabilities of AD-4833 in mice, rats, dogs, and monkeys were 81, 85, 94, and 81%, resp. The pharmacokinetics of AD-4833 in rats and dogs were linear in the dose ranges of 0.5-30 mg/kg and 0.1-3 mg/kg, resp. In rats, the radioactivity was distributed widely in tissues. The concns. of radioactivity in most tissues were lower than those in plasma. The main component in the tissues was the unchanged drug. During repeated administration of [14C]AD-483-HCl for 14 days to rats, the radioactivities in most tissues increased to attain a steady state within the last administration period. After ceasing the administration, 14C levels in tissues declined gradually. The binding of AD-4833 to plasma protein in mice, rats, dogs, and monkeys, and to serum protein in humans, was >98%. The drug was metabolized mainly to 6 compds., three of which were pharmacol. active. The main component in plasma was unchanged AD-4833 in mice, rats, and monkeys, and a metabolite in dogs. Only small amts. of unchanged drug were excreted in the urine and feces of mice, rats, dogs, and monkeys. The excretion of radioactivity in urine and feces was almost complete within 72, 72, 96, and 168 h in mice, rats, dogs, and monkeys, resp. Biliary excretion and enterohepatic circulation were observed in rats. In rats, the radioactivity was excreted quant. within 48 h after the end of repeated administration of [14C]AD-4833-HCl/day for 7 days. 14C was also detected in the milk of rats.

IT 112529-15-4, AD 4833
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(pharmacokinetics and metabolism of)

RN 112529-15-4 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-, hydrochloride (1:1) (CA INDEX NAME)



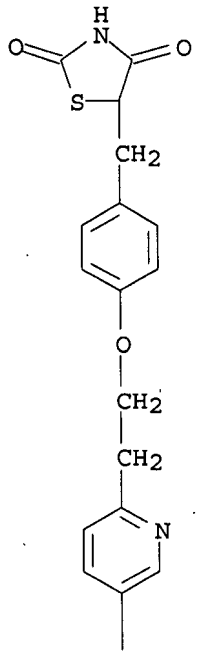
● HCl

IT 101931-00-4 146062-44-4 146062-45-5
146062-48-8 186751-40-6
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(pharmacokinetics and metabolism of antidiabetic AD 4833 in relation to formation of)

RN 101931-00-4 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)-2-hydroxyethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

L8 ANSWER 19 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1996:712946 CAPLUS
DOCUMENT NUMBER: 126:42525
TITLE: Synthesis and Biological Activity of Metabolites of the Antidiabetic, Antihyperglycemic Agent Pioglitazone
AUTHOR(S): Tanis, Steven P.; Parker, Timothy T.; Colca, Jerry R.; Fisher, Roberta M.; Kletzein, Rolf F.
CORPORATE SOURCE: Department of Discovery Chemistry, Pharmacia and Upjohn Inc., Kalamazoo, MI, 49001, USA
SOURCE: Journal of Medicinal Chemistry (1996), 39(26), 5053-5063
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 126:42525
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

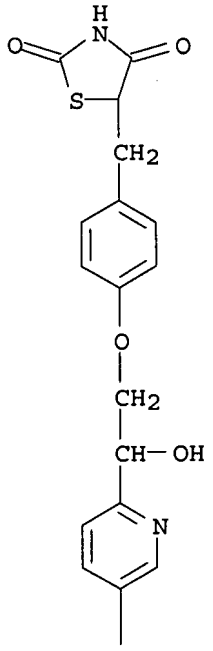
AB The authors have developed improved syntheses of pioglitazone metabolites I, II, III, and IV and the putative metabolite ketone V. These entities have been compared in the KKAy mouse model of human type-II diabetes to

pioglitazone. Ketone V has proven to be the most potent of these thiazolidinediones in this in vivo assay. When I-V were compared in vitro in the 3T3-L1 cell line to pioglitazone for their ability to augment insulin-stimulated lipogenesis, V was again the most potent compound with I, II, and IV roughly equivalent to pioglitazone. These data suggest that metabolites I, II, and IV are likely to contribute to the pharmacol. activity of pioglitazone, as had been previously reported for ciglitazone.

IT 101931-00-4P 111025-46-8DP, Pioglitazone, derivs.
146062-44-4P 146062-45-5P 146062-48-8P
146062-49-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and biol. activity of metabolites of antidiabetic antihyperglycemic agent pioglitazone)

RN 101931-00-4 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)-2-hydroxyethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A

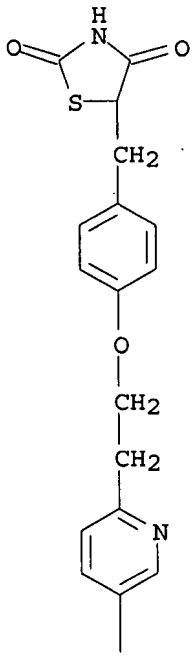


PAGE 2-A

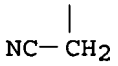
Et

RN 111025-46-8 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 20 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:320215 CAPLUS
DOCUMENT NUMBER: 125:48213
TITLE: Simultaneous quantitation of pioglitazone and its metabolites in human serum by liquid chromatography and solid phase extraction
AUTHOR(S): Zhong, W. Z.; Williams, M. G.
CORPORATE SOURCE: Drug Metabolism Research, Pharmacia & Upjohn, Inc., Kalamazoo, MI, 49001, USA
SOURCE: Journal of Pharmaceutical and Biomedical Analysis (1996), 14(4), 465-473
CODEN: JPBADA; ISSN: 0731-7085
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A high-performance liquid chromatog. (HPLC) method for the simultaneous determination of pioglitazone (U-72107) and its potential metabolites (M-1 to M-6) in human serum was developed. The method involved a solid phase extraction (SPE) of pioglitazone, its metabolites, and the internal standard (U-92573) from serum using C18 SPE columns with an elution solvent of 0.5 mL of acetonitrile-water (35:65, volume/volume). Separation of the eight analytes was achieved within 20 min using a reversed-phase Zorbax RC-C8 anal. column

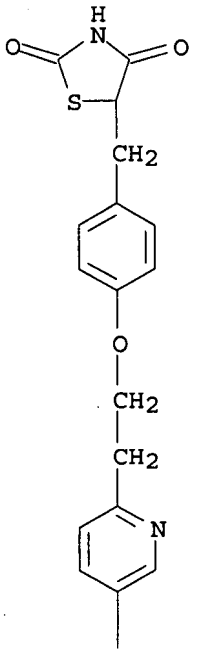
(250 mm + 4.6 mm i.d., 5 μm particle size) with a mobile phase of acetonitrile-water (40:60, volume/volume) containing 3 mL acetic acid per L mobile phase (apparent pH 5.5). An UV detector operated at 269 nm was used with a linear response observed from 0.02 to 2 μg mL-1 for these analytes except for M-4 which was best fitted with a polynomial regression. Limit of quantitation was 0.02 μg mL-1 for pioglitazone, M-3, M-5, and M-6; 0.04 μg mL-1 for M-2 and M-4; and 0.5 μg mL-1 for M-1 when using a 0.5 mL serum sample for extraction Obtained from the method validation, intra- and inter-assay precision was ≤9% and accuracy ranged from -8.2 to 13.4% for all analytes. The applicability of this method has been demonstrated by successfully analyzing clin. serum samples. The strategies in the HPLC characterization and in the SPE procedure development for this method are discussed as well.

IT 111025-46-8, Pioglitazone
RL: ANT (Analyte); ANST (Analytical study)
(simultaneous quantitation of pioglitazone and its metabolites in human serum by liquid chromatog. and solid phase extraction)

RN 111025-46-8 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A

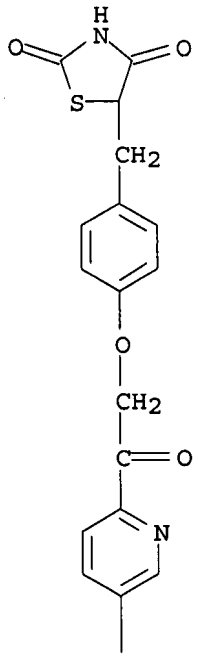


PAGE 2-A

Et

IT 101931-00-4 146062-44-4 146062-45-5
146062-48-8 146062-49-9
RL: ANT (Analyte); BSU (Biological study, unclassified); MFM (Metabolic formation); ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative)

PAGE 1-A



PAGE 2-A

L8 ANSWER 21 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:215289 CAPLUS
DOCUMENT NUMBER: 124:306331
TITLE: High-performance liquid chromatographic determination of pioglitazone and its metabolites in human serum and urine
AUTHOR(S): Yamashita, Kenji; Murakami, Hiromi; Okuda, Teruaki; Motohashi, Michio
CORPORATE SOURCE: Drug Analysis Pharmacokinetics Research Laboratories, Takeda Chemical Industries, Ltd., Osaka, 532, Japan
SOURCE: Journal of Chromatography, B: Biomedical Applications (1996), 677(1), 141-6
CODEN: JCBBEP; ISSN: 0378-4347
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A high-performance liquid chromatog. (HPLC) method for the simultaneous determination of pioglitazone and its metabolites (M-I to M-V) in human serum and urine was developed. The method for serum involved solid-phase and liquid-liquid extraction Urine with and without enzymic hydrolysis using β-glucuronidase was treated with liquid-liquid extraction The compds. in the extract were analyzed using HPLC with UV detection at 269 nm. The detection limits of pioglitazone, M-I, M-II, M-III, M-IV and M-V in serum were 0.01-0.05 μg/mL, those in urine were 0.1-0.5 μg/mL, and those in urine after enzymic hydrolysis were 0.3-0.5 μg/mL, resp. The method

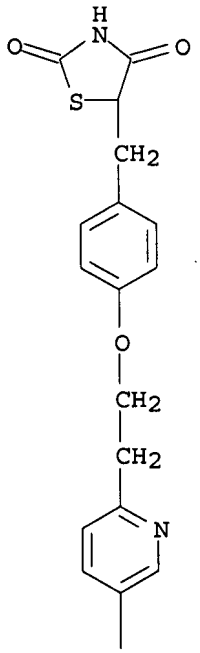
was applied to clin. trials of pioglitazone.

IT 111025-46-8, Pioglitazone
RL: ANT (Analyte); ANST (Analytical study)
(high-performance liquid chromatog. determination of pioglitazone and metabolites
in human serum and urine)

RN 111025-46-8 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

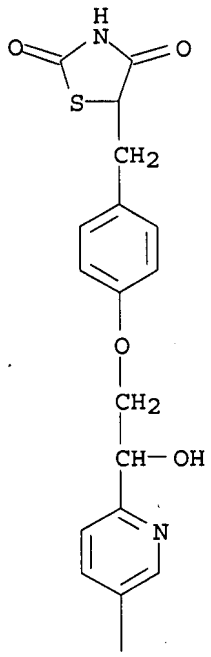
Et

IT 101931-00-4 176109-95-8 176109-96-9
176109-97-0
RL: ANT (Analyte); BSU (Biological study, unclassified); MFM (Metabolic formation); ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative)
(high-performance liquid chromatog. determination of pioglitazone and metabolites
in human serum and urine)

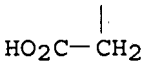
RN 101931-00-4 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)-2-hydroxyethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



L8 ANSWER 22 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:524543 CAPLUS
DOCUMENT NUMBER: 121:124543
TITLE: Disposition and metabolism of the hypoglycemic agent pioglitazone in rats
AUTHOR(S): Krieter, Philip A.; Colletti, Adria E.; Doss, George, A.; Miller, Randall R.
CORPORATE SOURCE: Department of Drug Metabolism, Merck Research Laboratories, Rahway, NJ, USA
SOURCE: Drug Metabolism and Disposition (1994), 22(4), 625-30
CODEN: DMDSAI; ISSN: 0090-9556
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The disposition and metabolism of [3H]pioglitazone was determined in male rats after oral administration. The peak plasma concentration of 10 μg/mL occurred 1 h after dosing at 10 mg/kg p.o.; the apparent plasma terminal half-life was 7.5 h. Most of the radioactivity in plasma ≤8 h after dosing was due to the parent drug. Pioglitazone was highly protein-bound in plasma; only 1-2% was free at concns. of 0.1-10 μg/mL. Within 3 days after oral administration to bile duct-cannulated rats, 36% and 15% of the oral dose was recovered in the bile and urine, resp. The pattern of biliary and urinary metabolites was similar. A total of eight metabolites were isolated and identified on the basis of NMR spectroscopy and MS. Metabolites resulting from hydroxylation of either carbon adjacent to the pyridine ring were conjugated with glucuronic acid or sulfuric acid. The metabolite hydroxylated on the terminal carbon of the Et side chain was

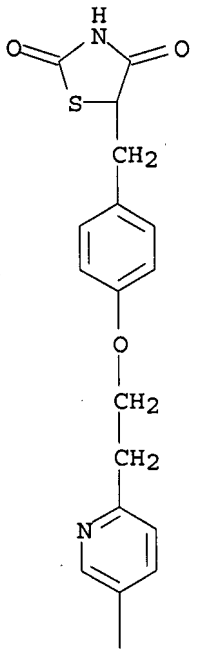
further oxidized to the carboxylic acid derivative Oxidative loss of the terminal carbon led to a nicotinic acid derivative and loss of both carbon atoms to the corresponding 3-hydroxypyridine derivative that was excreted as the sulfate conjugate. The two carboxylic acid metabolites were also conjugated with taurine.

IT 146062-44-4 146062-48-8 157142-90-0
157142-91-1 157142-92-2 157142-93-3
157142-94-4 157142-95-5 186751-40-6
RL: FORM (Formation, nonpreparative)
(formation of, as pioglitazone metabolite)

RN 146062-44-4 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-[5-(1-hydroxyethyl)-2-pyridinyl]ethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A



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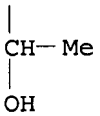
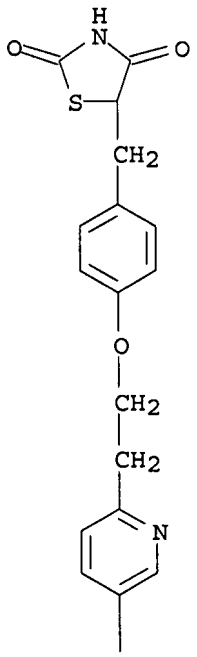


RN 146062-48-8 CAPLUS

CN 3-Pyridineacetic acid, 6-[2-[4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenoxy]ethyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

L8 ANSWER 23 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1993:472595 CAPLUS
DOCUMENT NUMBER: 119:72595
TITLE: Preparation of [[(pyridyl)ethoxy]benzyl]thiazolidinediones as antidiabetics
INVENTOR(S): Sohda, Takashi; Ikeda, Hitoshi; Greenfield, John C.; Colca, Jerry R.; Petzold, Edgar N.
PATENT ASSIGNEE(S): Upjohn Co., USA; Takeda Chemical Industries, Ltd.
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9218501	A1	19921029	WO 1992-US2566	19920406
W: AU, BB, BG, BR, CA, CS, FI, HU, KP, KR, LK, MG, MN, MW, NO, PL, RO, RU, SD, US				
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GN, GR, IT, LU, MC, ML, MR, NL, SE, SN, TD, TG				
CA 2106967	A1	19921012	CA 1992-2106967	19920406
CA 2106967	C	20031209		
AU 9217432	A	19921117	AU 1992-17432	19920406
EP 579733	A1	19940126	EP 1992-910028	19920406

EP 579733		B1	20010620			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, SE						
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AT 202352		T	20010715	AT 1992-910028		19920406
ES 2161692		T3	20011216	ES 1992-910028		19920406
JP 05086057		A	19930406	JP 1992-85405		19920407
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NO 9303615		A	19931008	NO 1993-3615		19931008
US 5441971		A	19950815	US 1993-137135		19931012
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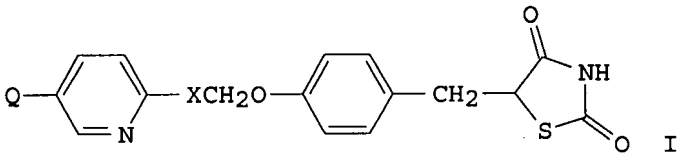
PRIORITY APPLN. INFO.:				JP 1991-78836	A	19910411
				WO 1992-US2566	A	19920406

OTHER SOURCE(S): MARPAT 119:72595

GI



I

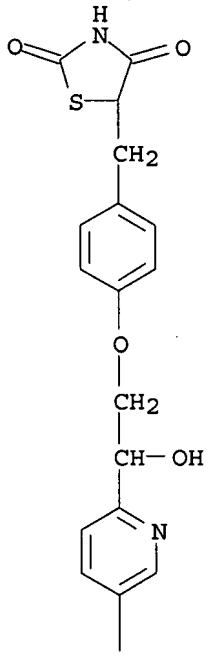
AB Title compds. I [X = CH2, CO; Q = Ac, MeCHOR, CH2CO2H; R = H, acyl; or Q = Et when X = CO] were prepared as antidiabetics and hypolipemics. Thus, cyclocondensation of Me 2-bromo-3-[4-[2-[5-(1-methoxymethoxyethyl)-2-pyridyl]ethoxy]phenyl]propionate (preparation given) with thiourea followed by deprotection then acetylation, gave title compound I [X = CH2; Q = Ac] (II). II at 0.005 weight% in chow diet for mice gave 56% reduction in blood sugar level and 43% reduction in plasma lipid level. Tablets containing I were prepared

IT 101931-00-4P 146062-44-4P 146062-45-5P
146062-46-6P 146062-47-7P 146062-48-8P
146062-49-9P 146062-50-2P 146062-51-3P
146062-52-4P 146062-53-5P 146062-54-6P
146062-55-7P 146062-56-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as antidiabetic)

RN 101931-00-4 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)-2-hydroxyethoxy]phenyl]methyl]- (CA INDEX NAME)

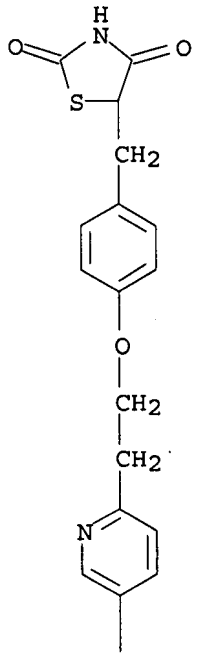
PAGE 1-A



PAGE 2-A

RN 146062-44-4 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-[5-(1-hydroxyethyl)-2-pyridinyl]ethoxy]phenyl]methyl]- (CA INDEX NAME)

PAGE 1-A



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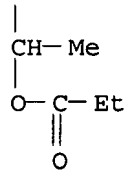
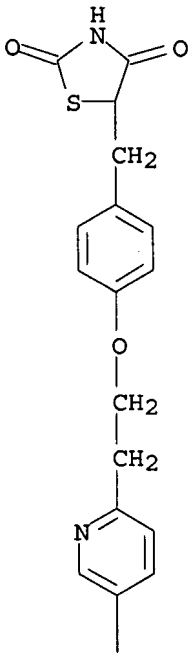
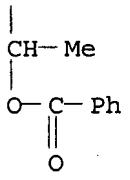


RN 146062-51-3 CAPLUS
CN Butanoic acid, 1-[6-[2-[4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenoxy]ethyl]-3-pyridinyl]ethyl ester (9CI) (CA INDEX NAME)

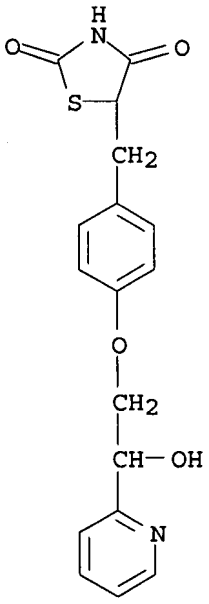
PAGE 1-A



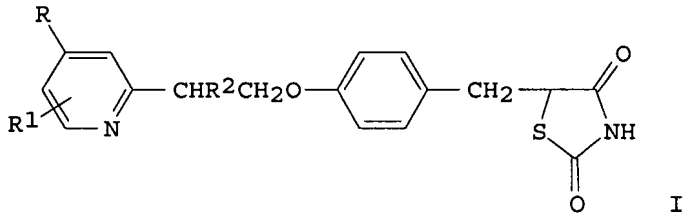
PAGE 2-A



L8 ANSWER 24 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1991:408602 CAPLUS
DOCUMENT NUMBER: 115:8602
TITLE: Studies on antidiabetic agents: synthesis and hypoglycemic activity of 5-[4-(pyridylalkoxy)benzyl]-2,4-thiazolidinediones
AUTHOR(S): Kees, Kenneth L.
CORPORATE SOURCE: Wyeth-Ayerst Res., USA
SOURCE: Chemtracts: Organic Chemistry (1991), 4(1), 82-6
CODEN: CMOCEI; ISSN: 0895-4445
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB The title research of T. Sohda et al. (1990) is reviewed with commentary and 11 refs.
IT 101931-05-9DP, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and hypoglycemic activity of)
RN 101931-05-9 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-hydroxy-2-(2-pyridinyl)ethoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



L8 ANSWER 25 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1990:423750 CAPLUS
DOCUMENT NUMBER: 113:23750
TITLE: Studies on antidiabetic agents. Synthesis and hypoglycemic activity of 5-[4-(pyridylalkoxy)benzyl]-2,4-thiazolidinediones
AUTHOR(S): Sohda, T.; Momose, Y.; Meguro, K.; Kawamatsu, Y.; Sugiyama, Y.; Ikeda, H.
CORPORATE SOURCE: Cent. Res. Div., Takeda Chem. Ind. Ltd., Osaka, 532, Japan
SOURCE: Arzneimittel-Forschung (1990), 40(1), 37-42
CODEN: ARZNAD; ISSN: 0004-4172
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 113:23750
GI



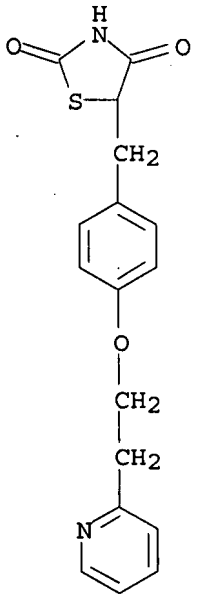
I

AB The synthesis of a series of title compds. I (R = H, Me, OH; R1 = H, 3-, 5-, 6-Me, 5-Et, 6-CH2OH; R2 = H, OH, CH2OH) is described. I were evaluated for hypoglycemic and hypolipidemic activities in genetically obese and diabetic mice. 2-(2-Pyridyl)alkoxy derivs. were found to have much better hypoglycemic and hypolipidemic activities than 2-(3-pyridyl)- and 2-(4-pyridyl)alkoxy derivs. or even the previously reported compound, ciglitazone. The introduction of a hydroxyl group at the 2-position of the ethoxy chain potentiated the activities. Among the potent compds.,

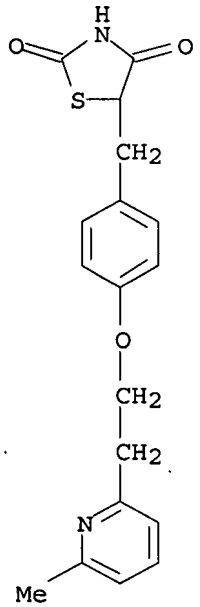
pioglitazone (AD-4833) was selected as a candidate for further study.

IT 74773-17-4 74773-19-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(hypoglycemic and hypolipidemic activity of)

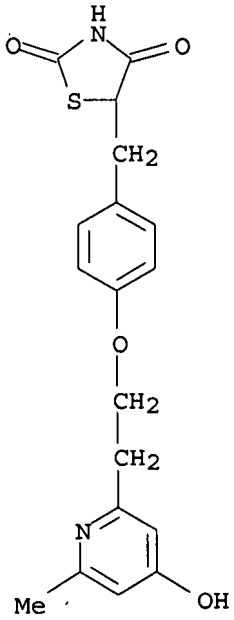
RN 74773-17-4 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(2-pyridinyl)ethoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



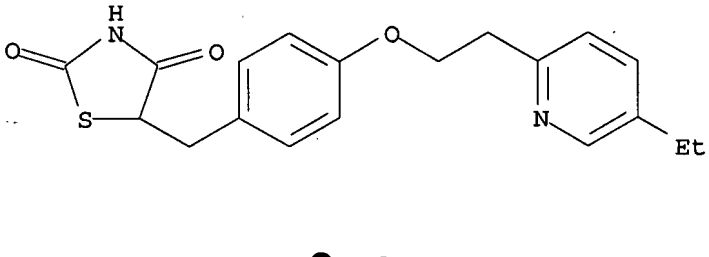
RN 74773-19-6 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(6-methyl-2-pyridinyl)ethoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)



IT 101930-98-7P 101930-99-8P 101931-00-4P
101931-04-8P 101931-05-9P 101931-06-0P



IT 112529-15-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 112529-15-4 CAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-, hydrochloride (1:1) (CA INDEX NAME)



● HCl

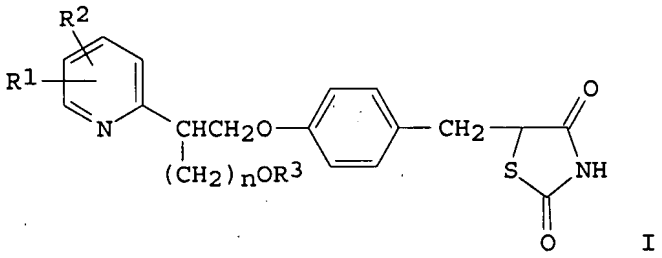
L8 ANSWER 26 OF 26 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1986:186401 CAPLUS
DOCUMENT NUMBER: 104:186401
TITLE: Thiazolidinedione derivatives, and their medicinal compositions
INVENTOR(S): Meguro, Kanji; Fujita, Takeshi
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd. , Japan
SOURCE: PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 8504171	A1	19850926	WO 1984-JP445	19840914

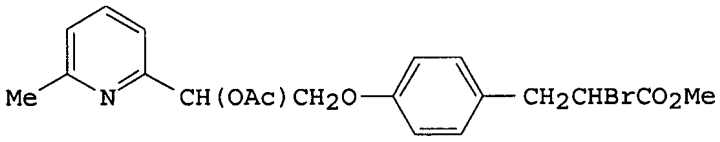
W: MC, US				
JP 60208980	A	19851021	JP 1985-41584	19850301
JP 05070633	B	19931005		
US 4582839	A	19860415	US 1985-711536	19850307
EP 155845	A1	19850925	EP 1985-301895	19850319
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
CA 1263961	A1	19891219	CA 1985-476976	19850320
PRIORITY APPLN. INFO.:			WO 1984-US117	A2 19840321
			WO 1984-JP117	A 19840321
			US 1984-624689	A2 19840611
			WO 1984-JP445	A 19840914

OTHER SOURCE(S): CASREACT 104:186401; MARPAT 104:186401

GI



I



II

AB The title compds. I (R1, R2 = H, alkyl; R3 = H, acyl; n = 0, 1) were prepared Thus, a mixture of 3.2 g the propionate II, 558 mg thiourea, 599 mL NaOAc, and 30 mL EtOH was refluxed for 4 h, 30 mL 6N HCl added, and the resulting mixture refluxed for 16 more hours to give 0.95 g I (R1 = 6-Me, R2 = R3 = H, n = 0). I decreased blood sugar and lipids by 22-53% or 11-58%, resp., in mice. I can be administered in the form of capsules, tablets, powders, etc.

IT 101930-98-7P 101930-99-8P 101931-00-4P
101931-01-5P 101931-02-6P 101931-03-7P
101931-04-8P 101931-05-9P 101931-06-0P
101931-07-1P 101931-08-2P 101946-34-3P
101946-35-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as hypolipemic and hypoglycemic agent)

RN 101930-98-7 CAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-hydroxy-2-(6-methyl-2-pyridinyl)ethoxy]phenyl]methyl]- (9CI) (CA INDEX NAME)